Reconsideration is requested of the objection to the specification for certain criticized informalities.

The specification has been amended to make clear that in Fig. 2 (page 7, lines 14 and 16), the two curves N.1 and N.2 refer to cell clone experiments effected in the presence per curve N.1 or in the absence per curve N.2 of different concentrations of RLX (i.e.,"relaxin"), and that in Fig. 3 (page 7, line 18), the same two clones N.1 and N.2 are referred to merely as 1 and 2, respectively.

Should the Examiner prefer, Fig. 3 can be amended to change "1" above the left listing "a b" to --N.1-- and "2" above the right listing "a b" to --N.2--, and line 18 of page 7 further revisedly amended to read --Fig. 3 shows the same two clones (N.1 and N.2) which were stimulated with--.

The specification has also been amended to make clear (page 9, lines 19 and 20) that Fig. 4A shows competitive PCR for IFN-γ on a representative cell clone in each instance, i.e., in one experiment in the upper panel and in another experiment in the lower panel, in the absence (upper lane of each panel) or in the presence (lower lane of each panel) of RLX.

In Fig. 4A, the asterisk below the upper panel and the asterisk below the lower panel merely indicate that there is an identical concentration between MIMIC and the sample, as noted in the legend below Figure 4 in col. 1 of page 2244 of the accompanying copy of Eur. J. Immunol. 1999, 29: 2241-2247 ("Piccinni-2241"), which is discussed more fully hereinafter.

The significance of such asterisks is not believed to be pertinent to the crux of the present invention. However, should the Examiner prefer, original page 9, line 20, can be amended by the Examiner, or by applicant in the next response if the Examiner so requests, by inserting after "10^{-8} M RLX for 12 h." the sentence --The asterisks indicate that there is an identical concentration between MIMIC and the sample.--

It is believed that the Examiner's stated objections to the specification have been overcome by the above noted amendments and explanations, and withdrawal of such objections is respectfully urged.

Reconsideration is requested of the Examiner's criticism of failure to comply fully with the sequence rules 37 CFR 1.821-825 in not referring in the disclosure to the required sequence identifier (SEQ ID NO:).

The specification has been amended (page 10, lines 3 and 4) to include the required SEQ ID NO: 1 and SEQ ID NO: 2 in the text. The Examiner is thanked for her helpful comments in this regard.

Accordingly, withdrawal of the Examiner's criticism of failure to comply fully with such sequence rules is believed to be in order.

Reconsideration is requested of the rejections under 35 USC 112, first paragraph, of the specification as being enabling only for relaxin but not for derivatives of relaxin, and of the claims as being based on a specification adequately descriptive of relaxin but not of derivatives thereof.

The accompanying copy of U.S. Patent No. 5,166,191, issued November 24, 1992 to Cronin et al. ("Cronin"), cited in U.S. Patent No. 5,952,296, issued September 14, 1999 to Mario Bigazzi, applicant herein ("Bigazzi-296"), confirms that the hormone relaxin ("RLX") is difficult to recover in pure form, being generally obtained as a crude aqueous extract from sow corpora lutea, and was only recently obtained as highly purified RLX from the ovaries of pregnant pigs, rats, sharks, and the placentas of horses and rabbits, with partially purified RLX being obtained from cow and human corpora lutea, placentas and decidua (col. 2, lines 15-35).

Per Cronin, mature human RLX is a disulfide bridged polypeptide hormone of approximately 6000 daltons, and exists in the human in the corpora lutea of pregnancy, in the non-pregnant female and in the male (seminal fluid), yet the obtaining of purified RLX preparations from human corpora lutea, placentas and decidua has not yet been demonstrated (col. 1, lines 8-13 and 49-52). Recombinant techniques have been applied to isolation of cDNA clones for rat and porcine RLX, and two human gene forms have been identified by genomic cloning, although only one such gene form, termed H2 relaxin, has been found to be transcribed in corpora lutea (col. 1, lines 53-68).

Cronin states that RLX consists of two peptide chains, referred to as A and B, joined by disulfide bonds with an intra-chain disulfide loop in the A-chain analogous to that of the hormone insulin, the two human RLX genes showing considerable nucleotide and amino acid sequence homology to each other, but with

notable regions of sequence divergence, particularly in the amino-terminal region of both A- and B-chains (col. 3, lines 1-8).

Indeed, Cronin notes that the structure of relaxin has apparently diverged considerably among species during evolution, with only 40-48% amino acid sequence homology existing among porcine, rat, shark and human RLX, yet in all species examined, the primary translation product of H2 RLX is a pre prorelaxin consisting of a 25 amino acid signal sequence followed by a B chain of about 29-33 amino acids, a connecting peptide of 104-107 amino acids (C peptide), and an A chain of 24 amino acids, with the further processing of the pro hormone obtained into RLX being not entirely understood (col. 3, lines 9-26).

Cronin confirms the art designated definition of "relaxin" as generally including polypeptides comprising the amino acid sequence of a naturally occurring (human or non-human animal, such as porcine, murine, etc.) RLX, or comprising an amino acid sequence which differs from such native RLX amino acid sequences by substitutions, deletions, additions and/or modifications of one or more amino acid residues in the A- and/or B-chains of the respective native RLX, as well as glycosylation variants, unglycosylated forms, organic and inorganic salts, and covalently modified derivatives of such native and modified peptides (col. 8, line 6, to col. 9, line 31; and col. 10, line 10, to col. 12, line 36).

At the same time, Cronin emphasizes the unpredictability as to medical uses of RLX in regard to various therapies there discussed, and the confusing results as to given medical uses that have been

obtained therewith (col. 4, line 21, to col. 5, line 29; and col. 17, line 38, to col. 18, line 13).

More to the point, present patent practice reinforces the acceptability of the term "relaxin or a derivative thereof" in that Bigazzi-296 was issued in 1999 with similar use of such tern in the claims (claims 1-37) thereof, and during the prosecution of the corresponding application of which Cronin was cited and applied. Bigazzi-296, like Cronin, also confirms that the structure of RLX, which is similar to insulin, is different for each species of animals and has been difficult to obtain in pure form (col. 1, lines 9-36), limiting the value of medical use test results therewith (col. 1, lines 37-40; and col. 2, lines 17-41), and emphasizing the unpredictability of its therapeutic use due to its dose-dependency (col. 8, lines 63-67; and col. 9, lines 19-24).

Hence, in the instant field of endeavor, in which in vivo physiological responses in humans are generally not as precisely observable as in vitro purely chemical responses in a laboratory, it is submitted that appropriate leeway is permissible in defining a physiologically active substance such as relaxin or a derivative thereof for a given medical use as contemplated herein.

It will be realized that despite the Examiner's skepticism, there is no presumption in this field of endeavor that derivatives of RLX do not function physiologically for given medical treatments in like manner to RLX itself, such that there is no need herein to rebut such a presumption. In fact, given the import of Cronin and Bigazzi-296, derivatives of RLX are considered in this art to

function physiologically for medical treatment purposes in the same way as RLX itself, absent some indicated reason to the contrary.

Thus, the term "relaxin or a derivative thereof" as used in the specification (p. 17, line 12, to p. 18, line 13) and claims (claims 1-6), is believed to be proper for describing the hormone RLX as contemplated herein.

Reconsideration is requested of the cognate rejection of the claims under 35 USC 112, second paragraph, as indefinite in being unclear whether a derivative is a modification, deletion, substitution and/or addition of a residue or nucleotide or other modification, and in not defining what is encompassed by the terms "Th2-dominated disease" and "pathogenic Th2 response" in the specification.

It is believed that in view of the state of the art as discussed above with regard to Cronin and Bigazzi-296 in connection with the rejections under 35 USC 112, first paragraph, the use of the term "relaxin or a derivative thereof" is acceptable herein.

It is also believed that in the context of the instant field of endeavor, the scope and import of "Th2-dominated disease" and "pathogenic Th2 response" are acceptable further patentably distinct medical uses under the present circumstances, especially in the light of the discussion hereinafter of the art as regards the obviousness-type double patenting rejection.

Withdrawal of the indefiniteness rejection under 35 USC 112, second paragraph, is accordingly urged.

Reconsideration is requested of the obviousness-type non-statutory double patenting rejection of the present invention (claims 1-5) as being unpatentable over claims 20-28 of applicant's recently issued (September 14, 1999) U.S. Patent No. 5,952,296 ("Bigazzi-296"), already made of record herein by applicant, in view of Piccinni et al., i.e., Annals of the New York Academy of Sciences: Neuroimmuno modulation 2000, 917: 844-852, "Environmental Factors Favoring the Allergen-specific Th2 response in Allergic Subjects," co-authored by Marie-Pierre Piccinni, Enrico Maggi and Sergio Romagnani ("Piccinni-844"), and which is a paper presented at the 4th International Congress of the International Society for Neuroimmuno modulation held on September 29-October 2, 1999 in Switzerland.

It is clear from the accompanying copy of the article Eur. J. Immunol. 1999, 29: 2241-2247, "Relaxin favors the development of activated human T cells into Th1-like effectors," Marie-Pierre Piccinni, Daniele Bani, Lucio Beloni, Cinzia Manuelli, Carmelo Mavilia, Franco Vocioni, Mario Bigazzi, Titiana Bani Sacchi, Sergio Romagnani and Enrico Maggi ("Piccinni-2241"), that the content thereof is essentially identical to that of the instant Bigazzi application in regard to the crux of the present invention.

Applicant's representatives abroad have advised that Piccinni-2241 was published July 7, 1999 or July 6, 1999, which of course was less than 1 year before the June 29, 2000 filing date of the instant Bigazzi application, and that the co-authors of Piccinni-2241 with Mario Bigazzi merely assisted him in his work but were

not co-inventors with him as regards the present invention, and thus Piccinni-2241 is not a valid reference herein under 35 USC 102 (b).

Piccinni et al., Annals of the New York Academy of Sciences: Neuroimmuno modulation 2000, 917: 844-852, "Environmental Factors Favoring the Allergen-specific Th2 response in Allergic Subjects," co-authored by Marie-Pierre Piccinni, Enrico Maggi and Sergio Romagnani ("Piccinni-844"), is a paper presented at the 4th International Congress of the International Society for Neuroimmuno modulation held on September 29-October 2, 1999 in Switzerland.

It is noted that the three co-authors of Piccinni-844, plus the instant applicant Mario Bigazzi, are among the ten co-authors of Piccinni-2241.

Piccinni-844 is only relevant to the extent of the statements on the lower half of page 847 thereof:

> "...Interestingly, we recently found that relaxin, another hormone produced by corpus luteum during pregnancy, also influences the cytokine profile of CD4+ effector T cells by upregulating the production of IFN-γ.[35]" (Emphasis added.)

That footnote 35, as shown on page 851 of Piccinni-844, cites Piccinni-2241 (i.e., Eur. J. Immunol. 1999, 29:2241-2247), which is essentially identical with the content of the instant Bigazzi application. Piccinni-2241, of overlapping co-authorship with Piccinni-844, is the best evidence that the concept of the instant

invention existed not only prior to the unspecified publication date in 2000 of Piccinni-844, but also necessarily prior to the September 29-October 2, 1999 time of such (assumably unpublished) 4th International Congress itself, which occurred abroad.

Thus, Piccinni-844, like Piccinni-2241, is not a valid reference herein, i.e., either under 35 USC 102 (b) or under 35 USC 102 (a), as the case may be.

Since the content of Piccinni-2241 is essentially identical to that at the crux of the instant Bigazzi application, and since the applicant herein, Mario Bigazzi, executed the declaration for patent herein on June 26, 2000 as sole inventor, after said July 7, 1999 or July 6, 1999 publication of Piccinni-2241, but within 1 year thereof, it is not believed that applicant Mario Bigazzi need furnish a declaration per 37 CFR 1.131 (Rule 131) stating that he alone earlier made the invention constituted by the content of the instant application and which is essentially identical to the content of Piccinni-2241, and which is self-evident from the fact that he executed the declaration for patent herein as sole inventor, and/or further stating that the co-authors of Piccinni-2241 merely assisted him in his work but are not co-inventors with him of the novel subject matter as disclosed and claimed herein.

Since Piccinni-844 is clearly not a valid reference herein, the double patenting rejection on the combination of Bigazzi-296 and Piccinni-844 cannot stand. Hence, there is no need to file a terminal disclaimer herein.

Claims 20-28 of Bigazzi-296 concern medical uses of RLX or a derivative thereof in regard to a method of treating a condition derived from the release of histamine involving (1) allergic rhinitis, (2) bronchial asthma, (3) anaphylactic disease, (4) pharmacological allergy, (5) alteration in tissue reaction, or (6) inflammation sustained by the release of histamine, by administering to a human exhibiting said corresponding condition an effective amount of RLX or a derivative thereof for preventing the release of histamine for relieving the given said condition (1), (2), (3), (4), (5) or (6), as the case may be.

On the other hand, claims 1-5 herein correspondingly concern medical uses of RLX or a derivative thereof in regard to a method of treating a Th2-dominated disease (claim 1), a method of inhibiting a pathogenic Th2 response (claim 2), a method of stimulating the development of activated human T cells into Th1-like effectors for treating a Th2-dominated disease (claim 3), a method of treating a Th2-dominated disease (claim 4), and a method of treating a Th2-dominated disease (claim 5), by administering to a human patient exhibiting said corresponding disease or response, an effective amount of RLX or derivative thereof for relieving said disease (claim 1), for inducing endogenous IFN-γ production for inhibiting said pathogenic Th2 response (claim 2), for stimulating said development (claim 3), for enhancing Th1 response of the immunological system of the patient for relieving said disease (claim 4), or for inducing endogenous IFN-γ production for relieving said disease (claim 5).

Absent pre-knowledge of the present invention, there would be no reason for the artisan aware of Bigazzi-296 to administer RLX or a derivative thereof to treat a condition as contemplated by the instant claims.

Indeed, even if a Bigazzi-296 patient being treated with RLX or a derivative thereof for (1) allergic rhinitis, (2) bronchial asthma, (3) anaphylactic disease, (4) pharmacological allergy, (5) alteration in tissue reaction, or (6) inflammation sustained by the release of histamine, also suffered from a condition such as that treated per one or more of instant claims 1-5, any inherent effect of the RLX or a derivative thereof for treating any such condition per one or more of instant claims 1-5 would go unnoticed but for hindsight use of the instant disclosure to show the way.

In sum, the art would not have the benefit of the present invention treatment method concept even if such method of use were inherently effected upon the Bigazzi-296 administering of RLX or a derivative thereof for the Bigazzi-296 taught treatment purposes.

Cronin, Bigazzi-296 and the instant invention perforce deal with correspondingly differing methods of treating patients in an imprecisely definable physiological environment unpredictable as to results, depending on the disease or dysfunction sought to be treated by the administered therapeutic agent at any given dosage, and the known and unknown side effects and possible complications attendant thereto, as peculiar to the individual patient.

There is no valid medical or physiological basis to presume that a Cronin patient suffering from one disease, e.g., heart

failure, and to whom RLX or a derivative thereof is administered to remedy that disease, or a Bigazzi-296 patient suffering from another disease, e.g., one of said conditions (1) to (6) deriving from the release of histamine, and to whom RLX or a derivative thereof is administered to remedy the given condition (1) to (6), inherently is a patient also suffering from a still different condition per instant claims 1-5.

Nor is there any valid medical or physiological basis to presume a Cronin patient or a Bigazzi-296 patient, to whom RLX or a derivative thereof is administered, would be thereby inherently treated to remedy a given condition per instant claims 1-5.

Merely because Bigazzi-296 shows that RLX or a derivative thereof is usable to treat said conditions (1) to (6) deriving from histamine release, would tell the artisan nothing about the instant methods of use of RLX or a derivative thereof.

Even if Bigazzi-296 patient also had a disease per instant claims 1-5, the effect on such patient consequent inherent action of use of RLX or a derivative thereof per the present invention would go unnoticed.

Methods of using RLX or a derivative thereof for the instant purposes (claims 1-5) would only be meaningful by impermissible hindsight use of the invention itself to show that it is not an invention.

Also, since there is no presumption in this field of endeavor that while RLX would be physiologically effective for a given purpose, a derivative thereof would not also be effective for the

same purpose, there is no need to rebut such presumption, absent evidence to the contrary.

It is impermissible for an Examiner to hold tacitly that inherent features and advantages of an invention are relevant to obviousness and somehow demonstrate that the invention is obvious, since inherency of an advantage and its obviousness are entirely different questions. In re Spormann, 150 USPQ 449, 452 (1966); In re Adams, 148 USPQ 742, 745-746.

It is equally impermissible to rely on the instant disclosure itself by hindsight, rather than on the prior art, to show lack of novelty or obviousness. In re Pavlecka, 138 USPQ 152, 154-155 (1963).

In view of the foregoing, the present invention is believed to be patentable over the pertinent prior art under 35 USC 102 and/or 35 USC 103, and the specification and claims are believed to be in permissible form and of adequately supported scope under 35 USC 112, first and second paragraphs, given the medical use and physiological context of the present circumstances, and the long known use of RLX and derivatives thereof for treating various diseases and conditions in humans.

Reconsideration and allowance are respectfully requested.

Favorable action is earnestly solicited.

Respectfully submitted
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PJF/E

Dated: August 30, 2001

Encl.: Marked-Up Pages 7, 9 & 10 From Specification
Copies of (2) References
PTO-144 Form
Petition for Two Month Extension of Time
Check for $195.00

IF THIS RESPONSE IS CONSIDERED FILED OUTSIDE A SHORTENED STATUTORY PERIOD SET OR NON-STATUTORY PERIOD, THE COMMISSIONER OF PATENTS AND TRADEMARKS IS HEREBY PETITIONED FOR AN EXTENSION OF TIME UNDER 37 CFR 1.136 (a) AND HEREBY AUTHORIZED TO CHARGE THE FEE REQUIRED, FOR THIS RESPONSE TO BE CONSIDERED TIMELY, TO OUR DEPOSIT ACCOUNT NO. 13-0410.

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BY: _____ August 30, 2001
MAIL CLERK DATE

in-house-made capture ELISA using anti IL-4 mAb bound to macrowell plates and biotinylated anti IL-4 mAb as revealing antibodies, respectively. Values of the cytokine content 5 SD over those of control supernatants obtained by stimulation of irradiated feeder cells alone were regarded as positive.

Fig. 1 shows the mean values (+SEM) of IFN-γ and IL-4 produced by TT-specific T cell cultures obtained in the presence of antigen plus 200 U/mL IL-12 as a function of RLX concentration. RLX increases the production of IFN-γ in TT-specific T cell lines as can be seen by the upper curve reported in Fig. 1, which increases with the concentration of RLX. On the other hand, no effect of RLX dilution can be observed on the production of IL-4.

Fig. 2 shows the increase of IFN-γ production in established $CD4^+$ T cell clones induced by RLX. The two curves (N.1 and N.2) shown in Fig. 2 relate to two $CD4^+$ T cell clones stimulated with immobilized anti-CD3 antibody in the presence (N.1) or in the absence (N.2) of different concentrations of RLX for 36 h.

Fig. 3 shows the same two clones (N.1 and N.2, referred to in Fig. 3 as 1 and 2, respectively) which were stimulated with immobilized anti-CD3 antibody in the absence (a) or in the presence (b) of 10^{-8} M RLX for 12 h. Total RNA was extracted as described hereinafter. 1 μg of RNA was reversed transcribed and cDNA were amplified and then subjected to PCR amplification with primers for IFN-γ and IL-4 as discussed more in detail below.

RNA extraction and RT-PCR

by ethidium bromide staining. The size of the amplified products was evaluated by comparison with molecular weight markers run in parallel lanes.

Competitive PCR

Competitive PCR for IFN-γ was performed using a competitor control fragment (PCR MIMIC; Clontech Laboratories Inc., Palo Alto, CA, USA) according to the manufacturer's instructions. PCR MIMIC was used together with sample cDNA in the reaction mixture; sample and control cDNA were amplified with the same primers, so they competed for the same primers in the same reaction, but were distinguished on gel electrophoresis by differences in length. By knowing the amount of PCR MIMIC added to the reaction, the amount of target cDNA and therefore the initial mRNA levels could be determined. Each sample (and competitor fragment) was subjected to 25 cycles of amplification as described above.

The results are shown in Figs. 4A and 4B. More particularly, Fig. 4A shows competitive PCR for IFN-γ performed on a representative $CD4^+$ T cell clone stimulated with immobilized anti-CD3 antibody in the absence (upper lane) or in the presence (lower lane) of 10^{-8} M RLX for 12 h. Fig. 4B shows the image analysis of the competitive PCR as described hereinafter.

Southern blot analysis

Southern blot analysis for IFN-γ was carried out with a "nested" probe designed to recognize intervening sequence between primers. This probe was obtained by PCR amplification. Primers

were selected using Oligo Primer Analysis Software Version 5.0 (National Biosciences, Inc., Plymouth, MN, USA): upper primer (227) SEQ ID NO: 1 CAGGTCATTCAGATGTAGCGGATA, lower primer (512) SEQ ID NO: 2 TCATGTATTGCTTTGCGTTGGAC (Genset, Paris, France). The DNA fragment of 286 bp amplified by PCR was subcloned using pGEM-T Vector system (Promega Co., Madison, WI, USA) according to the manufacturer's instructions, and sequenced. Sequencing of the subcloned product was performed using Sequenase version 2.0 DNA sequencing kit (USB, Cleveland, OH, USA). Southern blot was performed as disclosed by E.M. Southern, "Detection of specific sequence among DNA fragments by gel electrophoresis" in J. Mol. Biol. 1975, 98: 503-517.

The probe was labeled with a [^{32}P]deoxycytidine triphosphate using Megaprime DNA Labelling System (Amersham).

Figs. 5A and 5B show the results of Southern blot analysis. In Fig. 5A Southern blot analysis for IFN-γ was performed on four CD4$^+$ T clones (labelled nos. 1, 2, 3 and 4) stimulated with immobilized anti-CD3 antibody in the absence (a) and in the presence (b) of 10^{-8} M RLX respectively, for 12 h. Fig. 5B shows the image analysis of the four clones performed as disclosed hereinafter.

Image analysis

The intensity of the bands for β-actin obtained by RT-PCR was measured in all the samples to confirm that the same quantities of total RNA were reverse transcribed. In addition, the intensity of